MEDICAL STAFF CONFERENCE

The Clinical Spectrum of Meningococcal Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. EDELMAN:* The topic for discussion today is the clinical spectrum of meningococcal disease. The case presentation will be given by Dr. Klint.

DR. KLINT:† The patient was an 18-year-old Negro woman who two weeks before admission had been treated for gonococcal urethritis with one intramuscular injection of penicillin. However, she continued to have malaise, low-grade fever, and nasal congestion. Two days before admission she had severe cramping abdominal pain accompanied by nausea, vomiting, and persistent elevation of temperature. On admission the blood pressure was 90/30 mm of mercury, pulse 125 beats per minute and weak, respirations 30 per minute, and rectal temperature 38.5° C (101.2° F). The skin was cold and clammy and the patient complained of severe abdominal pain. No skin lesions or adenopathy were present. Except for pale conjunctiva no abnormality was noted on examination of the head and neck. There were no murmurs or rubs heard on auscultation of the heart, but an S_3 gallop was present. The chest and lungs were clear to auscultation and percussion. Periumbilical abdominal tenderness was present, but no guarding or rebound tenderness were noted. The remainder of the physical examination was within normal limits.

Leukocytes numbered 27,600 per cu mm with 79 percent polymorphoneuclear leukocytes. The hematocrit was 31.5 volumes percent. Serum sodium, potassium and chloride concentrations were within normal limits. The serum bicarbonate concentration was 19 mEq per liter; serum creatinine was 2.4 mg per 100 ml; and the amylase was 99 units on admission. Arterial blood gas studies revealed a pH of 7.0 and a CO_2 of 17.0 mm of mercury. The urine contained many white blood cells and a moderate number of bacteria per high power field. Slight cardiomegaly with increased pulmonary vascular markings were shown on an x-ray film of the chest. A plain film of the abdomen showed no abnormality. An electrocardiogram revealed supraventricular tachycardia.

The patient died of cardiac arrest seven hours after admission, the downhill course having been one of progressive cardiac irritability—multifocal premature ventricular contractions and intermittent episodes of ventricular fibrillation—and hypotension and metabolic acidosis. Resuscitative measures were unsuccessful.

Cultures of blood drawn before death grew group B Neisseria meningitidis. Autopsy re-

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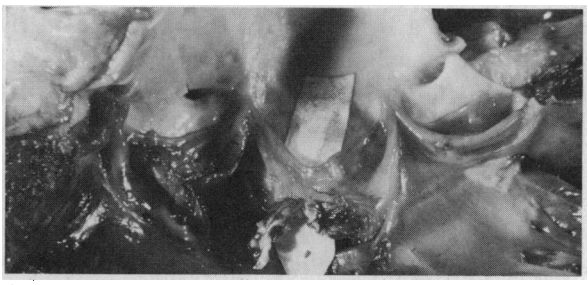

Figure 1.—Large perforation and destruction of aortic valve as found at autopsy.

vealed acute bacterial endocarditis. Two of the three aortic cusps were involved, with perforation of these valves and transection of one valve through the endocardium into the right atrium (Figure 1). There were also multiple areas of subendocardial necrosis and microabscesses in the papillary muscle. Gram staining of these areas did not reveal any organisms. Gram stain of the vegetation noted on the aortic valve did reveal acute inflammatory changes with Gram-negative intracellular diplococci.

DR. EDELMAN: Dr. John Conte will discuss this case.

DR. CONTE:* In 1948 Banks[1] emphasized the "protean nature of . . . . menigococcosis." I would like to discuss this case of acute endocarditis and sepsis as part of the clinical spectrum of disease caused by the meningococcus.

Route of Infection, Carrier State and Importance of Vaccination

The initial event in the pathogenesis of meningococcal disease is the entry and persistence of the organism in the nasopharynx, resulting in the carrier state. Although there is evidence for the existence of chronic carriers,[2] a given population appears to be in flux, with some persons becoming carriers, others losing their carrier state, and still others remaining noncarriers. For example, in a study of Air Force recruits at Lackland Air Force Base, material from 496 men was cultured on four different occasions, upon induction and then every two weeks during a six-week period.[3] Only five men (1.0 percent) had positive cultures on all four occasions. During the entire six-week period 362 men (78 percent) remained free of meningococci. The remaining 129 men (21 percent) either acquired

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TABLE 1.—Influence of Group A and Group C Polysaccharide Vaccine on the Percent of Recruits Who Acquired the Group C Carrier State

Company	*No Vaccine %*	*Group A Vaccine %*	*Group C Vaccine %*
B-6-3	42	37	24.0*
E-5-3	38	..	4.6**
E-2-3	69	68	31.0**

*P value less than 0.05 and **P less than 0.001 using the student "t" test

Adapted from Gotschlich *et al*[4]

TABLE 2.—Effectiveness of Group C Polysaccharide Vaccine on the Prevention of Group C Meningococcal Disease

Group	*Vaccinated Recruits*		*Nonvaccinated Recruits*	
	No. of Cases	*Rate**	*No. of Cases*	*Rate**
C	1	0.07**	38	0.70**
B	4	0.29	3	0.06

*Number of cases per 1000 recruits during an eight week period

**P less than 0.01

Adapted from Artenstein *et al*[5]

or lost their carrier status during the observation period.

Group C polysaccharide vaccine is known to increase serum bactericidal and hemagglutinating antibody titers and to decrease the carrier rate of Group C meningococcal organisms.[4] This effect is group specific since Group A polysaccharide vaccination had no effect on the Group C carrier state (Table 1). Recent field trials[5] have also demonstrated that Group C polysaccharide vaccination is 87 percent effective in preventing Group C meningococcal disease. This protective effect is also specific and does not alter the incidence of Group B meningitis (Table 2). A recent report demonstrated that 50 percent of patients with Group C meningococcal disease develop group specific hemagglutinating antibody in nasal washings.[6] This finding might indicate that increases in specific secretory IgA antibody occur and are associated with improved pharyngeal defense mechanisms.[4] Presumably by a similar mechanism, the carrier state itself is an immunizing process and natural immunity to meningococcal disease may result from intermittent carriage of the organism.[7] The sequence of events may therefore be that a noncarrier comes into contact with the meningococcus and either (1) remains a noncarrier because of previous immunity or (2) becomes a carrier. Subsequently, the carrier may lose the

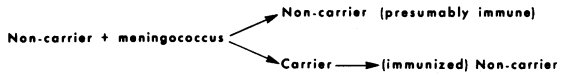

Chart 1.—Relationship between immunity and carrier status.

meningococcus and become an immunized noncarrier (Chart 1).

Clinical Spectrum of Meningococcal Disease

Wolf and Birbara[8] summarized the clinical aspects of 112 cases of acute meningococcal disease and described four different clinical entities on the basis of the presentation and clinical course. In their schema, however, categories for chronic meningococcemia and meningococcal endocarditis and pneumonia were not included. Chart 2 illustrates the entire spectrum of the disease, and each of these clinical entities deserves brief discussion. It should be emphasized that these are not fixed categories and that combinations obviously occur.[8]

Transient Bacteremia. The patient is admitted to hospital with an upper respiratory tract infection, suspected to be viral. The patient's condition improves within a few days, and he is discharged. Blood cultures taken during the time in hospital subsequently grow Neisseria meningitidis. The patient, however, remains well without specific treatment. There is apparently a transient bacteremia which is self-limited. Although this phenomenon is interesting from a pathogenetic standpoint, it presents no particular therapeutic problem.

Acute Meningococcemia. The patient presents with a sudden onset of symptoms, including fever, weakness, chills, nausea and vomiting. There may be a short history of pharyngitis or upper respiratory tract symptoms. The initial blood pressure may be normal, although in some cases hypotension, oliguria and acute renal failure occur. Usually there is a diffuse petechial rash or purpura. Fever is generally quite high (up to 41.5° C or 106° F), and leukocytosis is almost invariably present at some point in the course of the illness. The presence of leukopenia is a poor prognostic sign and is associated with a high fatality rate.[9,10] The fatality rate for acute meningococcemia in military series is reported to range from 5.5 to 7.1 percent. The fact that the rate is less than in civilian series probably results from a high index of suspicion and early treatment in military populations.

The pathogenesis of this fulminant form of acute meningococcal disease is not clearly understood. Earlier workers emphasized the finding of adrenal hemorrhage at autopsy and suggested that acute adrenal insufficiency may be responsible for the circulatory collapse—that is, the Waterhouse-Friderichsen syndrome. A number of lines of evidence do not, however, support this hypothesis: (1) attempts at laboratory confirmation of acute adrenal insufficiency have failed, (2) administration of steroids do not reverse the disease process, (3) survivors of this form of the disease do not have adrenal insufficiency, and (4) adrenal hemorrhage is not always present at autopsy in patients whose course has been typical for acute meningococcemia.[11]

The clinical findings of diminished plasma fibrinogen, factors V and VII, and thrombocytopenia, and the observation of fibrin thrombi at autopsy have suggested that disseminated intravascular coagulation may be a possible mechanism of shock, adrenal hemorrhage, and renal cortical necrosis. Heparin therapy has therefore been used to treat such cases and has reversed the *in vitro* coagulation abnormalities in a number of these cases. Some observers have also attributed clinical improvement to anticoagulation.[12] Others cast doubt on the value of heparin in this disease.[13] Controlled studies are not available, and the influence of anticoagulation on the morbidity and mortality of fulminant meningococcemia is not known.

Meningitis. The most common form of meningococcal infection is meningococcal meningitis. Although early workers thought that direct seeding of the central nervous system took place through the posterior nasopharynx,[14] it is now generally accepted that acute spread is from the nasopharynx into the blood stream and finally into the meninges. In the meningitic form of the disease, the patient complains of fever, headache and stiff neck. Usually there are neither petechiae nor ecchymoses. Blood pressure remains normal, perfusion is adequate, and renal failure does not develop. The spinal fluid is purulent and blood cultures may be positive. Response to penicillin is excellent, and the prognosis is better than in cases of acute meningococcemia.[9]

Meningoencephalitis. The patient presents in

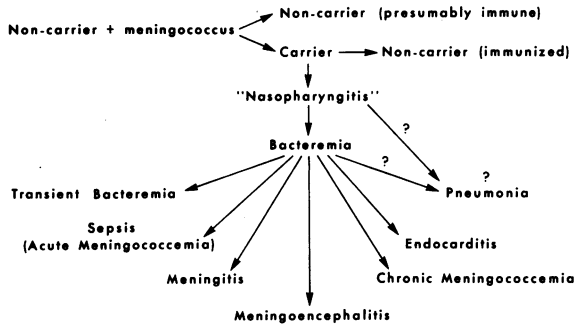

Chart 2.—The clinical spectrum of meningococcal disease.

a coma with deep tendon, superficial abdominal and cremasteric reflexes absent and extensor responses to plantar stimulation present. The spinal fluid is purulent and clinical meningitis is present. If the patient survives, coma subsides after a few days. Shock, renal failure, petechiae and ecchymoses are not usually a part of this syndrome.

Chronic Meningococcemia. This form of the disease is now rare. In 1963 Benoit[15] reported a case and reviewed an additional 148 cases which had been reported in the literature since the initial description in 1902. Since the advent of sulfonamides and antibiotics, chronic meningococcemia has become a vanishing disease, and many reviews in the past decade do not mention this diagnosis. The syndrome of chronic meningococcemia consists of prolonged intermittent or constant fever, arthralgias, arthritis, tenosynovitis, malaise, anorexia and weight loss. Petechial, hemorrhagic and erythema nodosa-like skin lesions may be present. This entity has often been confused with subacute bacterial endocarditis or rheumatic fever. The therapeutic response to the administration of sulfonamides or penicillin is usually dramatic.

Endocarditis. Subacute endocarditis resulting from meningococcus has been reported particularly in the earlier literature, but is now rare. Case reports are difficult to distinguish from descriptions of chronic meningococcemia and indeed in the previously mentioned series[15] there was evidence of bacterial endocarditis at autopsy in five of the ten fatal cases of chronic meningococcemia. Firestone[16] reviewed 24 cases of meningococcal endocarditis reported before 1946. However, the organism has virtually disappeared as a cause of subacute bacterial endocarditis in the last 25 years. Acute meningococcal endocarditis, at least as determined by autopsy, is also not common. In 1950 Daniels[11] reviewed the autopsy reports in 300 fatal cases of meningococcal disease. Fifty-two percent (151 cases) could be classified as cases of acute bacteremia. Endocarditis was found in none of these cases at autopsy. Myocarditis was found in 22 percent of the patients with bacteremia and adrenal hemorrhage and was found in the present case. Pericarditis is uncommon, but has been reported.[17]

Pneumonia. Primary meningococcal pneumonia, as a clinical entity separate from meningococcal sepsis, has been reported.[18] A recent systematic survey suggests that this entity may occur more frequently than generally appreciated.[19]

Classification of Present Patient

On the basis of the above categories, we shall attempt to classify the present patient. When the patient arrived at the emergency ward, she was not comatose and did not have a stiff neck. The meningoencephalitic and meningitic forms of the disease seemed unlikely, therefore, and indeed were not found at autopsy. The acuteness and ultimate fatal outcome would seem to exclude both a transient bacteremia and chronic meningococcemia. The wide pulse pressure, with a diastolic pressure of 30 mm of mercury, on admission was probably an indication of aortic valve insufficiency secondary to valve perforation. The progressive hypoperfusion syndrome and terminal cardiac failure were the result of both the meningococcal bacteremia and acute cardiac decompensation secondary to acute bacterial endocarditis and aortic insufficiency. Unfortunately, as in 20 percent of the fatal meningococcemia cases reported by Daniels,[11] the diagnosis was not appreciated ante mortem.

Prophylaxis and Treatment

Although an analysis of prophylaxis and treatment of meningococcal disease is beyond the scope of this discussion, current recommendations can be summarized:

- Sulfonamide prophylaxis has been abandoned because of the high incidence of sulfonamide resistance. Group B and C meningococci are emerging as the predominant organisms and as high as 70 percent of all isolates are resistant.

• There is an increased risk to close family contacts of patients with meningococcal disease. The rationale for use of prophylaxis for individual contact is unclear, and current public health recommendations discourage selective prophylaxis and emphasize case finding and early treatment. This is particularly important in light of the recent increase in sulfonamide resistance. Clinical illness has developed in contacts receiving prophylactic intramuscular penicillin.[20]

• House officers are not at increased risk.[21] When there is gross contamination of a contact, such as in mouth to mouth resuscitation, the contact should be observed carefully and treated with full therapeutic doses of penicillin if illness develops.

• Newer drugs have been tried to lower the carrier rate. Rifampin has been successful in a limited trial.[22] Penicillin, tetracycline and other antibiotics have either no effect on the carrier rate or have only transient, depressing effects.[23]

• Vaccination with group specific polysaccharide in the trials thus far has been successful and offers the greatest hope for control of this dread disease.

• The drug of choice is penicillin administered intravenously in the range of 20 million units per day. Cephalothin is not a suitable alternative since a number of treatment failures have been reported even when *in vitro* testing confirms that the organism is sensitive to the drug.[24] In the case of previous anaphylaxis to penicillin, the alternate drug of choice is chloramphenicol administered intravenously. Vague history of possible reaction or history of minor penicillin allergy should not preclude the use of this life-saving drug in this disease.

DR. EDELMAN: Are there any questions?

DR. FRIEDMAN:* David Rogers, in the last issue of *Yearbook of Medicine*, quotes an article which states that 70 percent of all people with meningococcemia show myocarditis at post mortem examination. I wonder if those who die of cardiovascular collapse might have myocarditis.

DR. CONTE: There is a very high incidence of meningococcal myocarditis at post mortem examination, and this may in fact be responsible for part of the circulatory collapse.

DR. JAWETZ:* Rifampin has been reported to be effective in the treatment of meningococcal carriers at the University of Wisconsin. I wonder if you would like to say, for example, that this is a drug that permits the very rapid emergence of resistance and perhaps it is for this reason that it would not be a good drug to use widely?

DR. CONTE: In limited trials rifampin has proved to be effective in decreasing the meningococcal carrier rate. Unlike penicillin, tetracycline, and other antibiotics which have failed to eradicate the carrier state, rifampin apparently is secreted in the nasopharynx in quantities sufficient to eradicate the organism. The usefulness of rifampin in mass prophylaxis is yet to be determined. Prophylactic antibiotic treatment of contacts of isolated cases in the general population has been suggested, but not documented to be a useful procedure. I think the emphasis should be on case finding and early treatment with full therapeutic doses of penicillin.

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